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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WRAP$_1$01		
International application No.	International filing date (*day/month/year*)	Priority Date (*day/month/year*)
PCT/IN 2004/000192	30 June 2004 (30.06.2004)	19 September 2003 (19.09.2003)

International Patent Classification (IPC) or national classification and IPC

IPC[8]: ***A61K 9/52*** (2006.01)

Applicant

SUN PHARMACEUTICAL INDUSTRIES LIMITED

1. This international preliminary examination report has been prepared by this International Preliminary Examination Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I. ☒ Basis of the opinion
   - II. ☐ Priority
   - III. ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV. ☐ Lack of unity of invention
   - V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI. ☒ Certain documents cited
   - VII. ☐ Certain defects in the international application
   - VIII. ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
9 March 2005 (09.03.2005)	24 February 2006 (24.02.2006)
Name and mailing address of the IPEA/AT Austrian Patent Office Dresdner Straße 87 A-1200 Vienna Facsimile No. 1/53424/200	Authorized officer KRENN M. Telephone No. 1/53424/435

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IN 2004/000192

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-8, 10, 12-24, as originally filed
pages _____, filed with the demand
pages 9, 11, filed with the letter of 26 November 2005 (26.11.2005).

☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages 25-26, filed with the letter of 26 November 2005 (26.11.2005).

☒ the drawings:
pages 1-5, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____.

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer-readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____.

☐ the claims, Nos. _____.

☐ the drawings, sheets/fig _____.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as „originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☒ the entire international application,

☐ claims Nos.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-16 are so unclear that no meaningful opinion could be formed *(specify)*:

The only technical features described in claims 1-16 in a concrete manner are the core comprising an active agent (opt. in admixture with either a swellable composition or a "reactive" composition and a coating surrounding said core. As there are myriad of formulations showing such a form, no meaningful search report can be established; thus the examiner has decided to carry out a search on the basis of the examples.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	----	YES
	Claims	1-16	NO
Inventive step (IS)	Claims	----	YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims	----	NO

Citations and explanations (Rule 70.7)

The present examination was carried out on the basis of the examples (see also "Non-establishment of the opinion"). In detail, the examination is focused on multilayered tablets containing either metoprolol or bupropion or oxybutynin and said tablets are coated with ethyl cellulose, wherein said coat provides an orifice.
Moreover, the so-called "design feature" (claims 1,16) is considered to be an equivalent to an orifice suitable to deliver an active agent (see also examples), because a product cannot be characterized by his behaviour in an aqueous environment.

In the light of this proviso the following documents still anticipate the subject matter of claims 1-16:
US 5681584 A shows a drug delivery device composed of (a) a core comprising a pharmaceutical, e.g. metoprolol, (b) a substantially soluble delay jacket, e.g. HPMC and (c) a semi-permeable membrane of ethyl cellulose providing a release orifice.

US 5650169 A refers to a trilayered tablet wherein the upper and the lower layer contains a drug in admixture with a polymer, e.g. HPMC and the intermediate layer is drug-free. The composition is coated by a polymeric film, e.g. ethyl cellulose providing a pore in the central circular area of the tablet.

GB 2140687 A discloses a delivery device comprising (a) a first composition comprising a beneficial agent (e.g. metoprolol), an osmagent and an osmopolymer, (b) a second composition comprising an osmagent and an osmopolymer, (c) a wall surrounding said bilayered composition and (d) a passageway in the wall communicating with the first composition and the exterior of the device.

US 2005/0008701 A1 concerns a controlled release pellet comprising (a) a water swellable inert core, (b) a drug layer applied to the inert core comprising metoprolol and a binder and (c) a controlled release coating containing a channelling agent, which surrounds the drug layer.

Industrial applicability is given.

WRITTEN OPINION

International application No.
PCT/IN 2004/000192

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 2005/0008701 A1	13.1.2005	11.7.2003	

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

(a) a core comprising an active ingredient composition comprising at least one active ingredient and a pharmaceutically acceptable excipient, and (b) a coating surrounding the core,

wherein the drug delivery system is designed in a manner such that the coating is reliably removed fully or partially from one or more preselected surfaces of the system upon contact with an aqueous environment, provided further that the coating is not removed from at least one of the surfaces.

Accordingly, the coating is partially removed from the system but may be fully or partially removed from one or more preselected surfaces. Hereafter, unless it is specified that the coating is removed from a surface the use of the term 'partial removal of coating' will refer to partial removal from the system.

The term "reliably" as used herein means that the coating is removed from the preselected surfaces and does not rupture from any other non-selected weak point in the coating. In contrast, prior art system disclosed in US 6,720,005 and US 6,733,784 rupture "mostly" around the belly-band area.

More particularly, the present invention provides an oral drug delivery system comprising –

(a) a core comprising an active ingredient composition comprising at least one active ingredient and a pharmaceutically acceptable excipient, and

(b) a coating surrounding the core,

wherein the oral drug delivery system is in the form of a coated tablet and includes a design feature such that the coating is removed partially or fully from one or more of the tablet surfaces upon contact with an aqueous environment, further wherein the design feature is such that it enables the selection of any of the tablet surface or surfaces from which the coating is desired to be partially or fully removed, provided further that the coating is not removed from at least one of the surfaces.

The oral drug delivery system of the present invention is designed such that the coating is removed <u>fully or</u> partially from a preselected surface or surfaces upon contact with an aqueous environment and not removed from at least one of the surfaces. The partial removal of the coating may be affected by several means and the design features enabling the same may be features of the coating or the core, or both, operating cooperatively. For example, the system may be designed ~~such that the~~ coating is ~~soluble~~ or <u>dissolved</u> from one surface of the system, but not dissolved from the other surfaces of the system, thus becoming partially removed from the system. Alternatively, the oral drug delivery system may be designed such that the coating is ruptured and removed fully or partially from one or more preselected surfaces of the system upon contact with an aqueous environment. As used herein the term "defective coating" refers to coatings that are susceptible to rupture due to a

a. a core comprising an active ingredient composition comprising at least one active ingredient and pharmaceutically acceptable excipients, and

b. a coating surrounding the core,

wherein the oral drug delivery system has at least two surfaces and is designed in a manner such that the coating is removed fully or partially from one of the surfaces when the oral drug delivery system contacts an aqueous environment and further wherein the coating is removed from the surface different from the one having the least surface area. The oral drug delivery systems of the present invention provide benefit over prior art systems which do not provide a flexibility in choice of the surface from which the coating can be removed, and generally expose the surface with the lower surface area.

Specific embodiments of the present invention also provide aforesaid oral drug delivery system, which release the drug without a substantial delay after the oral drug delivery system contacts an aqueous environment. The term "without a substantial delay" as used herein means that the active ingredient release is initiated from the controlled drug delivery system of the present invention within 0 to 60 minutes from the time the core contacts an aqueous environment, preferably within 0 to 20 minutes, and most preferably within 0 to 5 minutes.

In one embodiment of the present invention, the active ingredient composition is a swellable composition comprising at least one active ingredient and a swelling agent. In another embodiment of the present invention, the core comprises active ingredient composition and swellable composition, which may be present as one or more layers. The active ingredient present in these layers may be the same or different.

In one embodiment of the present invention the active ingredient is isolated from its environment by providing an oral drug delivery system comprising –

a. a core comprising the active ingredient and pharmaceutically acceptable excipients, and

b. a coating surrounding the core,

wherein the system has a design feature such that upon contact with an aqueous environment the coating ruptures to provide instant and rapid release of the active ingredient. Such systems are useful for active ingredients that are bitter in taste, or active ingredients that irritate the mucosal surface. Also, the system is useful for active ingredients that need to be protected from being degraded by contact with fluids from the surrounding environment.

CLAIMS –

1. An oral drug delivery system comprising -
   a. a core comprising an active ingredient composition comprising at least one active ingredient and a pharmaceutically acceptable excipient, and
   b. a coating surrounding the core,

   wherein the oral drug delivery system is in the form of a coated tablet and includes a design feature such that the coating is reliably removed fully from one or more of the tablet surfaces upon contact with an aqueous environment, further wherein the design feature is that the core further comprises a composition selected from a swellable composition and a reactive core composition located in the immediate vicinity of one or more preselected surfaces from which the coating is desired to be fully removed, provided further that the coating is not removed from at least one of the surfaces.
2. An oral drug delivery system as claimed in claim 1 wherein a further design feature is included in the coating.
3. An oral drug delivery system as claimed in claim 2 wherein the further design feature is that the coating on selected surface or surfaces of the tablet is selected from defective coatings and reactive coatings.
4. An oral drug delivery system as claimed in claim 3 wherein the further design feature is that the coating on selected surface or surfaces of the tablet includes one or more passageways in the coating on the selected surfaces.
5. An oral drug delivery system as claimed in claim 4, wherein the coating is impermeable to the active ingredient.
6. An oral drug delivery system as claimed in claim 1, wherein the active ingredient composition is present as one or more layers and the swellable composition is present as one or more layers.
7. An oral drug delivery system as claimed in claim 6, wherein the active ingredient present in the different layers may be the same or different.
8. An oral drug delivery system as claimed in claim 1, wherein the active ingredient composition is a controlled release composition.
9. An oral drug delivery system as claimed in claim 7, wherein one active ingredient composition is a rapid releasing composition and the second active ingredient composition containing the same active ingredient as the first active ingredient composition is a controlled release composition.

10. An oral drug delivery system as claimed in claim 1, wherein the swellable composition comprises a swelling agent.

11. An oral drug delivery system as claimed in claim 10, wherein the swelling agent is selected from the group comprising a swellable excipient, a gas generating agent and mixtures thereof.

12. An oral drug delivery system as claimed in claim 1, wherein the swellable composition comprises wicking agents.

13. An oral drug delivery system as claimed in claim 1, wherein the swellable composition comprises osmogents.

14. An oral drug delivery system as claimed in claim 1 wherein the drug release is initiated without a substantial delay after the oral drug delivery system contacts an aqueous environment.

15. An oral drug delivery system as claimed in claim 1 further comprising an outer coating of a pH-dependent polymer.

16. An oral drug delivery system comprising –

a core comprising an active ingredient composition comprising at least one active ingredient and a pharmaceutically acceptable excipient, and

b. a coating surrounding the core,

wherein the oral drug delivery system is in the form of a coated tablet and includes a design feature such that the coating is reliably removed partially from one of the tablet surface upon contact with an aqueous environment, further wherein the design feature is that the core further comprises a composition selected from a swellable composition and a reactive core composition in the form of an in-lay tablet located in the immediate vicinity of the preselected surface from which the coating is desired to be partially removed.